PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Can risk be predicted? An Umbrella Systematic Review of current Risk Prediction Models for Cardiovascular Diseases, Diabetes and Hypertension.
AUTHORS	Lucaroni, Francesca; Cicciarella Modica, Domenico; Macino, Mattia; Palombi, Leonardo; Abbondanzieri, Alessio; Agosti, Giulia; Biondi, Giorgia; Morciano, Laura; Vinci, Antonio

VERSION 1 - REVIEW

REVIEWER	Marc McRae National University of Health Sciences Lombard, Illinois, USA
REVIEW RETURNED	01-Apr-2019

GENERAL COMMENTS	There are numerous typographical errors which distract the reader from paying attention to the contents of the paper. This is especially too frequent in the results section.

REVIEWER	Tomasz Tomasik Department of Family Medicine, Chair of Internal Medicine and Gerontology, Jagiellonian University Medical College, Krakow, Poland I report personal fees from AbbVie, Eli Lilly Polska, Boehriger Ing, and non-financial support from VALEANT Polska.
REVIEW RETURNED	06-May-2019

GENERAL COMMENTS	A short personal summary of the manuscript and general comments. The Authors of the manuscript entitled “Can risk be predicted? An Umbrella Systematic Review of current Risk Prediction Models for Cardiovascular Diseases, Diabetes and Hypertension”, performed an overview of systematic reviews with the aim to compare the effectiveness of available risk prediction models (RPMs) for CVDs, hypertension and diabetes. The overview was carried out in accordance with the PRISMA guidelines. The Authors included 15 studies comparing different RPMs that met the inclusion criteria. The Framingham score and the QRISK score can be reasonably regarded as the gold standard for early identification of CVD.

	The purpose of this review is very worth undertaking but the current version of the paper fails to accomplish a clear overview of the topic. The way the study is presented is not convincing and rather difficult to read. Major comments including suggestions for improvement. 1.Aim of the study (page 2 and 3) The aim is not clear and differs between the protocol, the abstract and the main body of the manuscript. The review question in the protocol (PROSPERO: CRD42018088012) is: “Are current risk prediction models adequate for prediction of cardiovascular disease, diabetes or hypertension in adult general population?”. In the abstract it is: “…to compare the effectiveness of available RPMs…”, while in the main part of the manuscript it is: “to evaluate risk prediction models (RPMs) for CVDs, diabetes and hypertension, in order to assess which are the most effective tools in recognizing vulnerable people…”. Any deviations from the protocol that are in the manuscript should be listed and described in the additional file or in the Discussion section. 2. Abstract (page 2) In the description of the aim of the study, it is suggested that RPMs are used for the early recognition of CVDs, diabetes and hypertension, In my opinion, they are used to predict the probability (risk) that a person/patient with a given set of risk factors will experience the disease in the future. They can also be used to assist medical decision-making. For the early diagnosis of diseases, including screening in asymptomatic stage, other diagnostic methods are needed (e.g. a fasting blood glucose level in diagnosing diabetes). The Authors should pay attention and clarify this issue in the manuscript. 3. Article summary (page 2) There is a statement in the Article summery that “Publication bias and reporting bias could not be assessed”. I have doubts about it. To assess the selective outcome reporting within systematic reviews, one can compare those which were planned to be assessed in the systematic review protocols (or, if unavailable, in the methods section of the published report of SR) and the outcomes reported in the results section of the published report. To minimize publication bias, one can identify all relevant SRs included in the PROSPERO database and those that have not yet been published. 4. Introduction (page 3). I suggest shorten the information on the epidemiological data of CVDs, hypertension and diabetes presented in the Introduction section. 5. Discussion

	The Discussion section, in my opinion, does not have a proper structure. As recommended by PRISMA, I suggest starting from a summary of the main findings, their relevance for key groups, including physicians, then limitations, general interpretation of results in the context of other evidence, implications for future research and conclusions. I agree with the Authors on the strengths of the reviews, but I still have a suggestion to look more closely at the limitations. In addition to those described, the following should also be mentioned: (1) electronic search limited to three major international bibliographic databases and only English literature; (2) unrecognized gray literature with reports unpublished in the journals; (3) the search for ongoing and non-completed systematic reviews in the PROSPERO database has not been carried out, (4) no search for potential adverse effects of RPMs. I can't agree with the Authors that no other umbrella systematic reviews on risk prediction models for CVD are available (page 10). There are at least two overviews: (1) Collins DRJ, Tompson AC, Onakpoya IJ, et al. BMJ Open. 2017 Mar 24;7(3):e013650 and (2) Studziński K, Tomasik T, Krzysztoń J, et al. BMC Cardiovasc Disord. 2019 Jan 9;19(1):11. Although they had a different aim and focused on the effectiveness of using total CVD risk scoring in prevention, they can be mentioned in the discussion. Minor comments The abbreviations on page 5: ACU, C-STAt and D-STAT should be explained. The abbreviation of AUC (area under the curve) is given on page 8. There are also same minor mistakes in words, for example on page 5 the words "meettheinclusion" are written together and need improvement.

REVIEWER	Daniel T. Dibaba University of Tennessee, USA
REVIEW RETURNED	01-Aug-2019

GENERAL COMMENTS	The authors reviewed systematic reviews and meta-analyses on cardiovascular diseases, and diabetes risk prediction models. Having a validated risk predictor may help identify those at risk of the diseases and help in the prevention efforts. The authors recommended the Framingham risk score, ankle-brachial index , and QRISK score based models. Due to variability among the meta-analyses, the authors have not done a meta-analysis. The following are comments on the review: Introduction: Line 15-17: Please cite the sources of the data.

	Line 27-32: It would make the economic burden of the diseases clearer if the duration of the costs cited are specified. Are the listed costs annual costs or costs over several years? Method: You used figure 1 referring to two different things: the study selection process and PRISMA, Line 52 Figure 1 and Result Line 26 Figure 1. Under the assessment of study quality, on line 10 you mentioned, "...intervention type...". What are you referring to? How is intervention relevant to risk predictor models? At points, there are no spaces between words; for example, in Results Line 31, the words "…meettheinclusion…" may have been meant to be "…meet the inclusion…"; line 33, "…36remaining…" is another example. Results line 38: What "reviews293225" stand for is not clear. The description of the quality assessment may be improved. It begins with all the studies were of high-moderate quality but says 8 out of 15 were medium quality. If medium meant moderate, please be consistent in the use of words.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

1. There are numerous typographical errors which distract the reader from paying attention to the contents of the paper. This is especially too frequent in the results section.

Authors' reply:

We rectified the typographical errors according to the Reviewer's suggestion.

Reviewer #2:

1. Aim of the study (page 2 and 3)

The aim is not clear and differs between the protocol, the abstract and the main body of the manuscript. The review question in the protocol (PROSPERO: CRD42018088012) is: "Are current risk prediction models adequate for prediction of cardiovascular disease, diabetes or hypertension in adult general population?". In the abstract it is: "…to compare the effectiveness of available RPMs…", while in the main part of the manuscript it is: "to evaluate risk prediction models (RPMs) for CVDs, diabetes and hypertension, in order to assess which are the most effective tools in recognizing vulnerable people…".

Any deviations from the protocol that are in the manuscript should be listed and described in the additional file or in the Discussion section.

Authors' reply:

We edited the aim of the review and uniformed it throughout the manuscript according to the Reviewer's suggestions.

2. Abstract (page 2)

In the description of the aim of the study, it is suggested that RPMs are used for the early recognition of CVDs, diabetes and hypertension, In my opinion, they are used to predict the probability (risk) that a person/patient with a given set of risk factors will experience the disease in the future. They can also be used to assist medical decision-making. For the early diagnosis of diseases, including screening in asymptomatic stage, other diagnostic methods are needed (e.g. a fasting blood glucose level in diagnosing diabetes). The Authors should pay attention and clarify this issue in the manuscript.

Authors' reply:

We edited the above statement according to the Reviewer's suggestions.

3. Article summary (page 2)

There is a statement in the Article summery that "Publication bias and reporting bias could not be assessed". I have doubts about it.

To assess the selective outcome reporting within systematic reviews, one can compare those which were planned to be assessed in the systematic review protocols (or, if unavailable, in the methods section of the published report of SR) and the outcomes reported in the results section of the published report. To minimize publication bias, one can identify all relevant SRs included in the PROSPERO database and those that have not yet been published.

Authors' reply:

We assessed the publication bias and added a specific section for it, according to the Reviewer's suggestions.

4. Introduction (page 3).

I suggest shorten the information on the epidemiological data of CVDs, hypertension and diabetes presented in the Introduction section.

Authors' reply:

We believe that the epidemiological data are appropriate to be reported in such form, in order to give the most useful information to the scientists reading our work, irrespectively of their own background.

5. Discussion

The Discussion section, in my opinion, does not have a proper structure. As recommended by PRISMA, I suggest starting from a summary of the main findings, their relevance for key groups, including physicians, then limitations, general interpretation of results in the context of other evidence, implications for future research and conclusions.

Authors' reply:

We thank the Reviewer for the useful suggestion and we fully revised and edited our discussion section.

6. I agree with the Authors on the strengths of the reviews, but I still have a suggestion to look more closely at the limitations. In addition to those described, the following should also be mentioned: (1) electronic search limited to three major international bibliographic databases and only English literature; (2) unrecognized gray literature with reports unpublished in the journals; (3) the search for ongoing and non-completed systematic reviews in the PROSPERO database has not been carried out, (4) no search for potential adverse effects of RPMs.

Authors' reply:

We did our best to clarify the limitations of our study in the appropriate section, according to the Reviewer's suggestion.

7. I can't agree with the Authors that no other umbrella systematic reviews on risk

prediction models for CVD are available (page 10). There are at least two overviews: (1) Collins DRJ, Tompson AC, Onakpoya IJ, et al. BMJ Open. 2017 Mar 24;7(3):e013650 and (2) Studziński K, Tomasik T, Krzysztoń J, et al. BMC Cardiovasc Disord. 2019 Jan 9;19(1):11. Although they had a different aim and focused on the effectiveness of using total CVD risk scoring in prevention, they can be mentioned in the discussion.

Authors' reply:

We thank the Reviewer for the suggestion. We agree that the two studies have different aims from ours, but we found them extremely useful. Therefore, we included them both in the discussion section.

8. The abbreviations on page 5: ACU, C-STAt and D-STAT should be explained. The abbreviation of AUC (area under the curve) is given on page 8.

Authors' reply:

As suggested, we added the explanations, both in the text and in the captions.

9. There are also same minor mistakes in words, for example on page 5 the words "meettheinclusion" are written together and need improvement.

Authors' reply:

We rectified the typographical errors according to the Reviewer's suggestion.

Reviewer #3:

1. Introduction:

Line 15-17: Please cite the sources of the data.

Authors' reply:

We added the appropriate reference according to the Reviewer's suggestion.

2. Line 27-32: It would make the economic burden of the diseases clearer if the duration of the costs cited are specified. Are the listed costs annual costs or costs over several years?

Authors' reply:

The costs are yearly estimated; we edited the text accordingly.

3. Method:

You used figure 1 referring to two different things: the study selection process and PRISMA, Line 52 Figure 1 and Result Line 26 Figure 1.

Authors' reply:

We edited the sentence so that it is now referring to the study selection process only, according to the Reviewer's suggestion.

4. Under the assessment of study quality, on line 10 you mentioned, "...intervention type...". What are you referring to? How is intervention relevant to risk predictor models?

Authors' reply:

We were referring to the RPMs in the individual studies; the sentence was modified as requested and moved to the data extraction section.

5. At points, there are no spaces between words; for example, in Results Line 31, the words "…meettheinclusion…" may have been meant to be "…meet the inclusion…"; line 33, "…36remaining…" is another example.

Authors' reply:

We rectified the typographical errors according to the Reviewer's suggestion.

6. Results line 38: What "reviews293225" stand for is not clear.

Authors' reply:

We rectified the typographical error and removed the numbers, according to the Reviewer's suggestion.

7. The description of the quality assessment may be improved. It begins with all the studies were of high-moderate quality but says 8 out of 15 were medium quality. If medium meant moderate, please be consistent in the use of words.

Authors' reply:

We edited the phrasing so that it is now consistent throughout the paper, according to the Reviewer's suggestion.

VERSION 2 – REVIEW

REVIEWER	Tomasz Tomasik Jagiellonian University Medical College, Department of Family Medicine, Krakow, Poland Tomasz Tomasik has received personal fees from: Eli Lilly Polska, Boehringer Ingelheim, Novaris, and Shire.
REVIEW RETURNED	18-Nov-2019

GENERAL COMMENTS	Tomasz Tomasik has received personal fees from: Eli Lilly Polska, Boehringer Ingelheim, Novaris, and Shire. I believe that the article has been significantly improved by the authors. I accept the authors' explanations that the epidemiological

	data on CVD, HT and DM may be presented in a broader form. In my opinion, the article can be published.

REVIEWER	Daniel T. Dibaba University of Tennessee Health Science Center Tennessee Clinical and Translational Science Institute
REVIEW RETURNED	11-Nov-2019

GENERAL COMMENTS	The authors have satisfactorily addressed the comments raised in the previous version.